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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,693	BERLIN ET AL.	
	Examiner	Art Unit	
	Katherine Salmon	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6 and 8-15* is/are pending in the application.

4a) Of the above claim(s) *15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6, 8-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to papers filed 10/11/2007.

2. Currently Claims 1-4, 6, 8-15 are pending. Claims 5 and 7 have been cancelled. Claim 15 has been withdrawn.

3. The following rejections are reiterated or applied as necessitated by amendment. Response to arguments follows.

4. This action is FINAL.

Withdrawn Rejections

5. The rejections of the claims made under 35 USC 112/2nd paragraph are moot based on amendments to the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-4, 6, 8-14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the art does enable one of skill in the art to analyze cytosine

methylation in free floating DNA neither the art nor the specification enables one of skill in the art to determine the presence or absence of ANY cellular proliferative disease in a tissue, cell type or organ.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

Breadth of the claims

Claim 1 is drawn to obtaining a sample, determining an amount or presence of free floating DNA that originates form a particular tissue, cell type or organ comprising analyzing for a DNA methylation pattern that is characteristic for a particular tissue cell type or organ, and determining the presence of a cell proliferative disease based on the amount or presence of free floating DNA that originates from the particular tissue, cell type or organ. Claim 2 is drawn to obtaining a body fluid, determine the amount of total free floating DNA and determine the amount of free floating DNA that originates from a particular tissue cell type or organ comprising analyzing for a DNA methylation pattern that is characteristic for the tissue, cell type or organ. Claims 3-4 define the conditions. Claims 5-6 comprises a step of determining methylation pattern. Claim 8 defines the

sample. Claim 9 comprises a step of determining methylation pattern. Claim 10 is drawn to a method comprising determining abnormal level of free floating DNA to determine the presence or absence of a diseased condition. Claim 11 adds a methylation limitation step. Claim 12-13 comprises a method to determining diseased condition by detecting methylation of bound DNA. Claim 14 defines the measuring assay.

Nature of the Invention

The claims are broadly drawn to a method of determining any DNA methylation pattern for any tissue, cell type, or organ and detection of the presences of any cellular proliferative disease. The claims broadly encompass ANY diseased condition that originates from ANY tissue, cell type or organ. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Teachings in the Specification and state of the art

The specification asserts a means to predict which organ, tissue, or cell type has developed a medical condition, by employing means of distinguishing between DNA originating from different healthy or different diseased tissues, organs or cell types of the human body (p. 19 last paragraph). The specification asserts characteristic methylation patterns of certain genes can be positively correlated with specific

organs, tissues, and cell types (p. 19 last paragraph). However, the specification does not disclose an association in any individual, such as dog, cat, or peacock only human.

Further the specification does not provide a predicative association of the detection of any disease by the detection methylation patterns. It is unpredictable that any disease would be detectable in free floating DNA because it is unclear if any tumor, organ, or tissue can be detecting in a fluid sample. Therefore the skilled artisan would have to perform undue experimentation in order to determine the method steps needed to detect any tumor, organ, or tissue in a fluid sample and use this detection to determine disease status.

The specification asserts the knowledge achieved allows to predict if the individual carries a medical condition, such as a cell proliferative disease in said tissue, organ or cell type (p. 22 5th paragraph). The specification asserts a patient with a substantial amount of free floating DNA originating from liver, might have developed a liver tumor (p. 22 5th paragraph). The specification asserts that to validate this, the next step could be to employ, for example, a tailored test assay for disease indicating marker gene expression, specific for said organ or tissue (p. 22 5th paragraph). Therefore the specification asserts that validation studies are sometimes needed to clearly associate detection of free floating DNA with detection disease.

The specification asserts that methylation patterns found in the tested sample will be identified as belonging to a certain tissue, cell type or organ (p. 34 5th paragraph). The specification asserts that methylation patterns can be associated either by

comparing the individual data set resulting from said analysis to data received in previous studies or to a dataset obtained in a parallel experiment on one or preferably more control fluids (p. 34 last paragraph). The specification indicates that to determine if methylation patterns are associated with disease a comparison study must be done, however, the claims as broadly written, merely comprise the detection of methylation patterns.

Post filing art, Cottrell (clinical Biochemistry 2004 Vol. 37 p. 595) teaches that because methylation-based markers are not routinely used in clinical labs, the methodology has not been fully optimized, validated, and standardized. Cottrell et al. teaches that most of the methylation methods rely on bisulfite treatment protocol which must meet strict requirements for consistency and performance (p. 601 1st column 2nd full paragraph). Cottrell et al. teaches that in order to discover optimal markers and crease successful assays, there will need to be clearly defined clinical questions, sample sets, and methodologies coupled with the current methylation technologies (p. 601 1st column last paragraph).

Based on the data presented in the specification and the teachings in the art, it is unpredictable to correlate the methylation pattern of any free floating DNA to ANY disease condition by detecting methylation patterns (or merely detecting DNA). The art teaches the lack of predictability with regard to methylation pattern studies and correlation to any disease condition.

Figure 7 is disclosed in the specification as the result of the study wherein DNA methylation pattern of specific CpGs in DNA from four different tissues has been

analyzed (p. 42). The specification discloses that methylation analysis from CpG positions correlate to the specific tissue types (p. 43). However, the art teaches that using circulating DNA as a diagnostic tool is unpredictable and that methylation patterns are not reproducible.

Ziegler et al. reviewed literature related to the diagnostic potential of circulating DNA (Cancer Treatment Reviews, 2002 Vol. 28, pp. 255). Ziegler et al. state that fraction of plasma DNA contributed by tumors varies from 3-93%, undermining their utility as diagnostic tool (p 256, last paragraph). Ziegler et al. stress the need for standardization and selection of patients for the studies (p 257, 2nd paragraph). Ziegler et al. also teach that the studies performed to date show variable levels of correlation between circulating DNA levels and cancer (Table I; page 257, last paragraph; page 259, first and second paragraphs). Ziegler et al. also reviewed references related to the determination of gene hypermethylation in circulating DNA of patients with cancer. They teach that even though some genes like APC, methylation of which is present in 96% of lung cancers, enable prediction of patient survival, methylation of other genes was shown to be not significantly associated with the presence of cancer in patients with non-small cell lung cancer (NSCLC) (p 261, last paragraph), and contradictory results were obtained for other cancers as well (p 262).

In summary, the claims encompass the detection of any disease using samples from any individual by the detection of free floating DNA or the detection of methylation patterns of free floating DNA, however, the specification does not provide guidance as to how to make associations between any disease in any individual by the detection of

free floating DNA. Moreover, the specification indicates that the correlation of disease and free floating DNA must have an association step to compare to a normal individual and a validation study. The associations are unpredictable, because the specification provides no statistically significant association between any disease and detection of free floating DNA, further the art teaches that theses associations are unpredictable.

The predictability or unpredictability of the art and degree of experimentation

The art teaches genetic variations and associations are often irreproducible and that there are many parameters that need to be evaluated prior to using a genetic test to determine a disease. Hirschhorn et al. (Genetics in Medicine. Vol. 4, No. 2, pages 45-61, March 2002) teaches that most reported associations are not robust. Of the 166 associations studied three or more times, only 6 have been consistently replicated. Hirschhorn *et al.* suggest a number of reasons for the irreproducibility of studies, suggesting population stratification, linkage disequilibrium, gene-gene or gene-environment interactions, and weak genetic effects and lack of power are possible factors that lead to such irreproducibility. Hirschhorn *et al.* caution that the current irreproducibility of most association studies should raise a cautionary alarm when considering their use as diagnostics and prognostics (p. 60, Col. 2). Thus, Hirschhorn cautions in drawing conclusions from a single report of an association between a genetic variant and disease susceptibility.

The art teaches that there is unpredictability in associating circulating DNA (free floating) with disease. The post-filing art, Bremnes et al. (Lang Cancer 2005 Vol 49 p.

1) teaches a review of circulating DNA in lung cancer by evaluating the role of circulating DNA in 22 studies (abstract). Bremnes et al. teaches the analysis of circulating DNA in plasma might lead to increasing clinical impact, however, large perspective clinical studies are needed to validate and standardize any test for DNA alteration in plasma or serum of high risk individuals or patients with established lung cancer (Abstract). Therefore there is still unpredictability with correlating circulating DNA in plasma and serum with disease condition.

Jung et al. (Cancer Letters 2004 Vol 205 p. 173) teaches the presence of circulating DNA (free floating) in patients with prostate cancer and benign prostate hyperplasia (BPH) (abstract, page 174-175 1st two paragraphs). Juang et al. teaches that patients with metastases had higher levels of circulating DNA, the DNA levels in cancer patients without metastases were not significantly different from the normal controls, whereas some of the BPH patients had circulating DNA levels higher than normal (p. 175-176 and Figure 2). Jung et al. teaches that plasma DNA (free floating) has a limited validity as metastatic marker in prostate cancer patients (Abstract).

As evidenced by current literature, circulating DNA is not always correlated with the presence of cancer in a subject. Sidransky et al. (Ann. NY Acad. Sci.;2000 vol. 906, pp. 1), the origin of circulating DNA in the blood is uncertain (page 3, second paragraph), and "these studies raise significant issues about the biology and physiology of how the DNA is released and maintained in the circulation and ultimately on its clinical value" (page 3, third paragraph). Sindransky states further "However, it is abundantly clear that large prospective studies with longitudinal follow up are essential if

we are to carefully evaluate these circulating DNA markers and eventually integrate them into the clinical setting."

The current art teaches that methylation is not only caused by neoplasms, but that methylation can be detected in normal tissue. This indicates that detection of methylation does not indicate neoplasic tissue. The current art teaches detection of methylation is indicative of not only neoplasm but also aging of normal cells. Yates et al. (Oncogene 2006 Vol 25 p. 1984) teaches that methylation increases with age and malignancy (abstract). Yates et al. teaches that methylation was detected in urine DNA from patients with and without bladder cancer (Abstract). Yates et al. teaches aberrant methylation is not cancer specific and can be found in a normal ageing cell population (p. 1985 1st column 1st paragraph). Yates et al. teaches the overall knowledge of the molecular mechanisms of DNA methylation in health and cancer remains poor and one uncertainty is the extent of aberrant DNA methylation in nonmalignant tissue and the association between ageing and aberrant DNA methylation (p. 1985 last paragraph).

Amount of Direction or Guidance Provided by the Specification

The specification does not provide any specific guidance as to how to correlate detection of any disease by the detection of free floating DNA. The specification discloses that a correlation to disease must include an association step to compare methylation patterns to individuals and a validation study to confirm detection of disease.

The art teaches detection of disease with methylation patterns in free floating DNA is

unpredictable and that these associations need to be confirmed by multiple large sampling sizes to determine a clear association. The skilled artisan, therefore, would have to perform undue experimentation to determine the correlation of disease detection to detection of free floating DNA as it is broadly written in the claims.

Working Examples

The specification provides no examples to correlate detection of disease by detection of free floating DNA in any individual. Example 1 describes determining plasma blood from one patient to detect neoplastic disease (p. 43). The specification asserts that it was concluded a significant portion of the DNA in the patient's blood derived from his lung, the physician now referred the patient to a hospital that is specialized on inflammatory or cell proliferative diseases of the lung. However, the specification does not provide any pvalue, therefore, it is unclear how to extrapolate the example of one specific patient to the detection of a large portion of DNA derived from lung to the detection of any disease by detection of free floating DNA.

The specification asserts three more patient samples with detection of serum DNA levels (p 43-44), however there are no working examples showing an statistically significant association of any disease. The first three experiments only had an association of a specific patient and a specific disease, whereas it is unclear the number of patients in the 4th experiment.

Furthermore, the specification provides no indication as to whether the detection of a methylation pattern is significant such that the skilled artisan would be able to predictably correlate the results which any disease condition. The specification does not have an example of determining in ANY sample a correlation of methylation pattern with detection or ANY diseased condition.

Therefore, though the specification provides a few studies of the correlation of one patient and the detection of one tissue type and as presented in figure 7 the correlation of specific CpG island methylation patterns and tissue type, the art as discussed above teach that these associations are unpredictable. The art teaches that the correlation of methylation patterns to any disease in any given population is not reproducible. The skilled artisan, therefore, would have to perform undue experimentation in order to determine if methylation patterns in circulating DNA is correlative to any disease.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since there is significant number of parameters, which would have to be studied prior to being able to practice the claimed invention as broadly as written. The skilled artisan would have to determine the association of any detection of disease with measurement of free floating DNA. The skilled artisan would then have to determine if this association was species base. This would require significant inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of Skill in the Art

The level of skill in the art is deemed to be high.

Conclusion

Case law has established that '(t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed

invention without 'undue experimentation.'" *In re Wright* 990 F.2d 1557, 1561. *In re Fisher,* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that '(t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the Court in *Genetech Inc. v Novo Nordisk* 42 USPQ2d 1001 held that '(I)t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the specification does not provide any predictable association of detection of free floating DNA and any disease. Further the art teaches that the measurement of free floating DNA and associations made are unpredictable. In view of this unpredictability, the specification has not established that the presently claimed method can be used to determine the detection of any disease by the detection of free floating DNA or methylation patterns of free floating DNA.

Accordingly, in view of the unpredictability in the art, and the lack of disclosure in the specification and in the prior art and the unpredictability of the art, it would require undue experimentation for one of skill in the art to make and use the claimed invention.

Response to Arguments

The reply traverses the rejection.

(A) The reply asserts that the method is not to be understood as the "determining

the amount of or presence of free floating DNA" but the "determining the amount of or presence of fee floating DNA, which originates from a specific tissue, cell type, or organ" which is a subpart of the total amount of free floating DNA (p. 10 last paragraph). The reply asserts that the step of recognition of methylation patterns of tissue, cell type or organ characteristic methylation is independent of disease (p. 10 last paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

The examiner agrees that the claims are drawn to determining the amount or presence of free floating DNA which originates from a specific tissue, cell type, or organ, however, the claims are drawn to detecting the presence of a cellular proliferative disease. The detection is unpredictable because the detection of free floating DNA from tissue, cell, or organ types are not predictably associated with a cellular proliferate disease. For example, Yates et al. teaches that methylation was detecting in urine DNA from patients with and without bladder cancer (abstract). Yates et al. teaches the methylation pattern was not cancer specific and can be found in a normal aging cell population. Therefore the art discloses that though methylation patterns originating from cells can be detecting in fluid samples, these samples are not always correlative to cellular proliferative disease. In the instant case it is unpredictable that detecting free floating DNA originating from a particular tissue, cell type, or organ would detect the presence of cellular proliferative disease because the free floating DNA originating from a particular tissue, cell type, or organ detected in the fluid does is not always associative to cellular proliferative disease.

The methylation is independent of the disease, however, the claims are drawn to detecting the cellular proliferative diseases and not merely detection of the source of the

free floating DNA.

(B) The reply asserts that the invention is not centered on direct correlation of disease type with methylation pattern, but rather a correlation of organ, tissue, or cell type methylation patterns (p. 11 1st paragraph). The reply point to 3 post filing references (Human Epigenome Project, Eckhardt et al. and Raykan et al.). The reply asserts increased levels of DNA have been correlated with presence of cell proliferative disease by a disease shedding DNA into the blood stream or other body fluids (p. 11 1st paragraph). The reply asserts it is only by recognizing the potential of the organ specific methylation patterns for the identification of the source of free floating DNA that the inventive method provides for a correlation of increased levels of specific-organ derived DNA with presence of cell-proliferative disease of said specific organ(p. 11 1st paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

It is first noted that the three postfiling references were not submitted with the reply. Eckhardt et al. and Raykan et al. have been placed on record with the submission of these articles in the 892. Further, the first page of the Human Epigenome Project has been printed out, but it is noted that the information on the website is continually updated.

The art presented shows the unpredictability of determining the methylation profiles of organs and tissues for comparison to detect cellular proliferation. Eckhardt et al. teaches methylation patterns for three human chromosomes from a representative number of healthy human tissues and primary cells (p. 1378 2nd column 1st paragraph).

Eckhardt et al. teaches methylation patterns are influenced by a number of endogenous and exogenous parameters (p. 1381 1st column last paragraph). Eckhardt et al. teaches that tissue samples may be inherently more heterogeneous than primary cells because of the different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph). Therefore the postfiling art teaches determining a methylation pattern that is characteristic for a particular tissue, cell type or organ to detect the presence of a cellular proliferative disease is unpredictable. Eckhardt et al. teaches that different profiles can be obtained depending on the age. Eckhardt et al. teaches that the profile of some tissues contains heterogeneousity because of the varying cell types in the tissue.

Raykan et al. et al. teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore Raykan et al. teaches that there is a high degree of variability between individual patients therefore it is unpredictable that there is a DNA methylation pattern that is characteristic for a particular tissue, cell type, or organ without determining the differences in the methylation patterns between individuals. In other words, it would be unpredictable that the level of free floating DNA detected was from a particular tissue type or from differences between individuals.

(C) The reply lists an example to illustrate the inventive method (p. 11 1st paragraph). Body fluid sample analysis to detect total free floating; detection is made that the corresponding patient is suffering from a cell proliferative disease; methylation analysis of total free floating DNA reveals such specific methylation patterns based on comparison of methylation pattern detected with methylation patterns known to be characteristic for several organs; quantitative analysis revels level of lung derived DNA in total amount of free floating DNA is increase; deduction is made that the lung of said patient is suffering from a disease and spreading DNA into the body fluid (p. 11 steps A-E).

This argument has been thoroughly reviewed but has not been found persuasive.

The method steps do not require that the corresponding patient have a cell proliferative disease. As discussed in argument B it is unpredictable that the methylation pattern of an organ is the same in all patients. The art teaches that there is variability in methylation patterns depending on age, if there is a disease present, and developmental stage. Therefore the methylation profile of the patient compared to the control methylation patterns might differ for reasons other than tissue or organ type. The reply is assuming that free floating DNA from an organ, tissue, or cell type is only present in the blood when the patient is suffering from a disease, however, Yates et al. teaches that methylation was detecting in urine DNA from patients with and without bladder cancer (abstract). Yates et al. teaches the methylation pattern was not cancer specific and can be found in a normal aging cell population. Therefore the art discloses that though methylation patterns originating from cells can be detecting in fluid samples,

these samples are not always correlative to cellular proliferative disease.

(D) The reply asserts that the claims have been amended to recite cell proliferative disorders for which it is concluded that an organ or tissue affected by such a disorder will shed DNA into a body fluid where it can be detected (p. 12 1st paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

The reply is assuming that free floating DNA from an organ, tissue, or cell type is only present in the blood when the patient is suffering from a disease, however, Yates et al. teaches that methylation was detecting in urine DNA from patients with and without bladder cancer (abstract). Yates et al. teaches the methylation pattern was not cancer specific and can be found in a normal aging cell population. Therefore the art discloses that though methylation patterns originating from cells can be detecting in fluid samples, these samples are not always correlative to cellular proliferative disease.

(E) The reply asserts that that it is not necessary to detect the presence of a disease because tissue specific methylation patterns are a recognized part of the art and one of ordinary skill in the art can correlated the obtained methylation pattern to published ones (p. 12 2nd paragraph). The reply asserts the mere detection of an increased amount of lung specific methylation pattern in DNA obtained from a body fluid would be sufficient to conclude that the individual suffers from a lung cell proliferative

disorder (p. 12 2nd full paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

There is an unpredictability that just because the sample detected has a specific methylation pattern of a specific tissue that there is a detection of a disease. Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore the association between detecting a methylation pattern of a tissue and the detection of cellular proliferative disease is unpredictable because the methylated tissue could be due to other factors.

(F) The reply asserts that circulating DNA as a diagnostic tool is predictable that that there are a number of clinically valid studies published (p. 12 last paragraph). The reply points out that Abott spend an amount of money to develop molecular diagnostic methylation marker for early diagnosis of colon cancer (p. 12 last paragraph). The reply asserts that Epigenomics has demonstrated in multiple clinical case control studies with blood plasma samples from colorectal cancer patients, healthy controls and patients with non-cancerous colon diseases that methylated DNA of Septin 9 shed by tumors into the blood stream can serve as a biomarker for the sensitive and specific detection of colorectal cancer (p. 13 1st paragraph). The reply points to an Abstract in the ECCO conference wherein the poster presented reports on a study wherein a series of matched urine and plasma samples were analyses (p. 13 1st paragraph). The reply

asserts that methylation markers that discriminate prostate cancer patients from healthy controls were identified (p. 13 1st paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

The reply points to evidence in the art of companies such as Abott and Epigenomics with circulating DNA as a diagnostic tool. This information is not in the cited reference and therefore the Attorney's arguments cannot take the place of evidence on the record. As stated in the MPEP, 2106 "Arguments of Counsel"

"However, it must be emphasized that arguments of counsel alone cannot take the place of evidence in the record once an examiner has advanced a reasonable basis for questioning the disclosure. See In re Budnick, 537 F.2d at 538, 190 USPQ at 424; In re Schulze, 346 F.2d 600, 145 USPQ 716 (CCPA 1965); In re Cole, 326 F.2d 769, 140 USPQ 230 (CCPA 1964). For example, in a case where the record consisted substantially of arguments and opinions of applicant's attorney, the court indicated that factual affidavits could have provided important evidence on the issue of enablement."

This should not be construed as an invitation for providing evidence. As further stated in the MPEP 716.01 regarding the timely submission of evidence:

A) Timeliness.
Evidence traversing rejections must be timely or seasonably filed to be entered and entitled to consideration. In re Rothermel, 276 F.2d 393, 125 USPQ 328 (CCPA 1960). Affidavits and declarations submitted under 37 CFR 1.132 and other evidence traversing rejections are considered timely if submitted:
(1) prior to a final rejection,
(2) before appeal in an application not having a final rejection, or
(3) after final rejection and submitted
(i) with a first reply after final rejection for the purpose of overcoming a new ground of rejection or requirement made in the final rejection, or
(ii) with a satisfactory showing under 37 CFR 1.116(b) or 37 CFR 1.195, or
(iii) under 37 CFR 1.129(a).

In the instant case the reply points to diagnostic tools made by Abott and

Epigenomics that have show diagnosis of patients. However, this does not support enablement of a predictive association of methylation patterns in circulating DNA to detection of any cellular proliferative disease. Though some diagnostic methods do work, the correlation of methylation pattern to a disease is unpredictable. As shown by Yang et al. methylation patterns are associated with age differences. Further as shown in the reply the method is not towards merely a correlation of methylation to disease, but a correlation of methylation pattern of a tissue, cell, or organ to the methylation pattern of free floating DNA to detect cellular proliferative disease.

(G) The reply asserts that with respect to the correlation between tissue specificity and methylation applicant refers to Adorjan et al. which describe the correlation of specific methylation patterns for healthy tissue (p. 12 last paragraph). The reply points to the Human Epigenome Project give evidence for the fact that tissue specific methylation exists independently of disease status (p. 13 last paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

The examiner again points applicant to arguments of counsel in MPEP 2106 as discussed in point F.

Adorjan et al. does screen several hundred CpG sites in 76 samples form four different human tissue types to correspond to healthy controls to discriminate CpG to differentiate tissue types (abstract). Adorjan et al. teaches that methylation between prostate and kidney cell was distinct (p. 7 1st paragraph). However, Adorjan et al. does not teach that methylation patterns between any tissue, cell type, or organ is distinct.

Eckhardt et al. teaches that tissue samples may be inherently more heterogeneous than primary cells because of the different cell types constituting a given tissue (p. 1382 1st column 2nd paragraph). Eckhardt et al. teaches that some tissue such as lung and colon will show a stronger correlation between age and methylation (p. 1382 1st column 2nd paragraph).

Therefore the art teaches that such distinctions of tissue types must be examined to produce a characteristic profile.

(H) The reply asserts that that Ziegler et al. deals with problems with cancer markers as opposed to tissue or organ markers (p. 14 1st full paragraph). The reply asserts the number of lung cancer cells is much smaller than the number of affected lung cells which might be shed into the blood and hence detection of lung cancer DNA might be more difficult than the detection of lung tissue DNA.

The reply asserts that fact that some "other genes were shown to not be significantly associated with the presence of cancer" and the contradictory results are not surprising because the methods previously used either had false positive and negatives (p. 14 3rd paragraph).

The reply asserts that Jung et al. underline the importance of the inventive method (p. 15 1st full paragraph). The reply asserts the problem in the state of the prior art may be regard as the limited information that is achievable form detecting the total amount of free floating DNA in plasma however the inventive method overcomes the problem by providing for a method to determine the origin of the free floating DNA (p. 15

1st full paragraph).

The reply asserts that because of the fact circulating DNA is not always correlated with the presence of cancer the claims have been amended to not comprise the detection of the absence of the disease (p. 15 2nd full paragraph). The reply asserts that is no report known showing that elevated levels of circulating DNA predominantly derived from a specific organ was detecting in a perfectly healthy individual (p. 15 2nd paragraph).

The reply asserts that the problems Sidransky et al. teaches about detecting the origin of circulating DNA is what the method overcomes (p. 15 2nd full paragraph). The reply asserts the method determined not only whether tissue specifically methylated DNA is present but whether it occurs in a body fluid indicating disease state of the tissue or organ (p. 15 last paragraph). The reply asserts hat fact that aging effects methylation patterns should be taken into consideration when designing the experiments to identify tissue specific makers however it is not relevant for the inventive method which makes use of tissue specific makers (p. 15 last paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

However it is still unpredictable that the detection of lung cells in blood is correlative to detection of a cellular proliferative disease. As taught by Yates et al., cells in blood from tissue can be due to aging of the tissues.

However, there is still unpredictability in determining the origin of the cell will detect the presence of a cellular proliferative disease.

In the instant case it is unpredictable that detecting free floating DNA originating

from a particular tissue, cell type, or organ would detect the presence of cellular proliferative disease because the free floating DNA originating from a particular tissue, cell type, or organ detected in the fluid does is not always associative to cellular proliferative disease.

(I) The reply asserts that a conclusion cannot be drawn that the skilled artisan would have to perform undue extermination to determine the correlation of disease detection of a specific organ or tissue to detect the organ or tissue specific free floating DNA (p. 16 3rd paragraph). The reply assert the correlation has to be made that lung specific methylation patterns detected on circulating DNA in blood samples correlated to a disease lung and that the skilled artisan would be able to draw this conclusion without undue experimentation (p. 16 3rd paragraph).

This argument has been thoroughly reviewed but has not been found persuasive.

The instant claims are not enabled. The claims are drawn to obtaining a fluid from a human and determining an amount or presence of free floating DNA that originates from a particular tissue, cell type or organ in a sample comprising analyzing for a DNA methylation pattern that is characteristic for the particular tissue, cell type, or organ. This step is unpredictable because the specification has not provided guidance as to the methylation pattern that is characteristic for any tissue, cell type, or organ. Each methylation pattern for each tissue, cell type, or organ would have to be determined. It is unpredictable that a methylation pattern can be formed for each tissue, cell type, or organ which could be used to determine if the amount or presence of free

floating DNA is from a particular tissue, cell type or organ because Raykan et al. et al. teaches that of the analyzed CpG sites 80% of the displayed methylation levels that varied by more than 20% between individuals and/or tissues (p. 2171 2nd column last paragraph). Raykan et al. teaches that DNA methylation profiles are complex and dynamic and can vary with developmental stage, tissue type, age, the alleles parent of origin, and disease state (p. 2176 last paragraph). Therefore methylation profiles have a high degree of unpredictability and vary between individuals.

Therefore the comparison of a sample in one patient to a profile might indicate that there is a high level of certain methylation sites, however, this methylation pattern could be due to developmental stage, age, and disease state of the patient.

Further, even if one could detect a particular methylation profile to any tissue, cell, or organ type, this detection in the blood could be due to other factors such as aging (see Yates et al.) and therefore would not detect the presence of a cellular proliferative disease.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-8, 10-11, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Goessl et al. (Cancer Research 2000 Vol. 60 p. 5941).

With regard to Claim 1, Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation).

Goessel et al. teaches determining the presence of free floating DNA that originates from a particular cell type (abstract). Goessel et al. teaches determining the presence of prostate cancer cells in bodily fluids (abstract).

Goessel et al. teaches analyzing the DNA methylation pattern that is characteristic for a particular cell type and determining the presence of a cell proliferative disease based on the presence of free floating DNA that originates from a particular cell type. Goessl et al. teaches determining the presence of GSTP1 (DNA from prostate tumor cell) (Abstract). Goessl et al. teaches determining the presence of prostate cancer (a disease) based on the presence of GSTP1 in bodily fluids (Abstract).

Goessl et al. teaches determining the presence of free floating DNA from a particular tissue in the sample comprising analyzing DNA methylation pattern that is characteristic for the particular tissue type (Figure 3). In Figure 3

Claim 2 is identical in scope to Claim 1 except that Claim 2 has a further limitation of determining the amount of total free floating DNA and the amount of free floating DNA that originates from a particular tissue, cell type, or organ. With regard to Claim 2, Goessl et al. teaches a methylation specific PCR technique (MSP)which detects 200 prostate cancer cells (free floating DNA originating from a cell type) in 2.2 X 10^7 nonmalignant leukocytes (total DNA) in a blood sample (p. 5942 second column 1st full paragraph).

With regard to Claims 3-4, Goessl et al. teaches that the free floating DNA was modified by bisulfite treatment (chemical treatmen) beforee detection of the amount or presence of DNA was determined (p. 5941 last paragraph).

Goessl et al. teaches detection of a methylation pattern to determine the presence of DNA from prostate tissue (abstract).

With regard to Claim 6, Goessl et al. teaches the MSP technique to determine methylation patterns unique to the GSTP1 gene to determine that this gene is in the bodily fluids (abstract and p. 5941-5942 Fluorescent MSP).

With regard to Claim 8, Goessl et al. teaches plasma, serum, ejaculate, and urine fluids (Abstract).

With regard to Claim 14, Goessel et al. teaches a PCR detection method (amplification procedure with subsequent determination of amount of product amplificate formed (p. 5941-5942 Materials and Methods).

Response to Arguments

The reply traverses the rejection. (A) The reply asserts that Goessl et al. differs from the claimed method because GSTP1 is a nucleic acid which bears a methylation pattern that is for a specific type of carcinoma and not as a marker for the prostate organ (p. 17 1st full paragraph). (B) The reply asserts that that GSTP1 detects cancer not tissue types (p. 17 1st full paragraph). The reply asserts that the instant method differs because it is detecting the tissue or organ methylation pattern (p. 17 last 2 paragraphs). (C) The reply asserts that the steps of determining a methylation pattern

characteristic of a particular tissue, cell type or org by determining the amount of DNA that exhibits a tissue, cell type or organ characteristic DNA methylation pattern.

These arguments have been fully considered but have not been found persuasive.

(A) And (B) Though Gossel et al. does not teach detection the presence of free floating DNA that originates from a particular tissue or organ, the claims as amended are not limited to only detection of a particular tissue or organ. The claims are also drawn to determining the presence of free floating DNA that originates from a cell type. Detection of GSTP1 would detect the presence of DNA from a cell type (e.g. cancer cell). Therefore Gossel et al. teaches all the limitations of the claims.

(C) Gossel et al. does not teach determining the amount of DNA that is exhibited in a particular cell type. Therefore the rejections made in the previous office action with regard to Claims 10—13 are withdrawn.

8. Claim 9 is rejected under 35 U.S.C. 102(b) as being anticipated by Goessl et al. (Cancer Research 2000 Vol. 60 p. 5941) as evidenced by Rein et al. (Nucleic Acids Research 1998 Vol. 26 p. 2255).

Goessl et al. teaches obtaining plasma, serum, ejaculate and urine from patients (abstract and p. 5941 Patients and Methods DNA Isolation). Goessl et al. teaches determining the presence of GSTP1 (DNA from prostate tumor tissue) (Abstract). Goessl et al. teaches determining the presence of prostate cancer (a disease) based on the presence of GSTP1 in bodily fluids (Abstract). Goessl et al. teaches that the free

floating DNA was modified by bisulfite treatment (chemical treatment, methylation) before detection of the amount or presence of DNA was determined by MSP (methylated PCR) (p. 5941 last paragraph). With regard to Claim 9, Rein et al. teaches that bisulfite treatment converts all unmethylated cytosines in the DNA into uracil but leaves position 5-methylated cytosines unmodified (Table 1 and Figure 2).

Response to Arguments

The reply traverses the rejection. The reply asserts that Goessl et al. does not teach detecting the presence of a cellular proliferative disease in a cell type. This has been thoroughly reviewed but has not been found persuasive. As discussed in the 35 USC 102(b) rejection above, Goessl et al. teaches all the limitations of the independent claims wherein Goessel et al. teaches determining the presence of a cellular proliferate disease in a cell type.

Conclusion

1. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not

mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

2. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Katherine Salmon whose telephone number is (571) 272-3316. The examiner can normally be reached on Monday-Friday 8AM-430PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Katherine Salmon
Examiner
Art Unit 1634

/Jehanne Sitton/
Primary Examiner
12/14/2007